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Operative Techniques in
Orthopaedics

Cell and Biomimetic Scaffold-Based Approaches for Cartilage Regeneration

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This article discusses tissue engineering approaches in the repair of focal cartilage defects and degenerative joint conditions. It introduces the traditionally applied methods and provides a look at newer clinical and preclinical cell-based therapies for these treatments. In addition, cutting-edge approaches, both on the cellular front and the scaffold fabrication front, are examined for potential clinical application. Finally, the article closes with a look at future perspectives and directions in studying and understanding degenerative joint diseases.
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Introduction—The Need for Cartilage Tissue Engineering

Articular cartilage is the clear, white, and smooth connective tissue that covers opposing joint surfaces. The main functions of the articular cartilage are mechanical—to allow frictionless motion and to absorb and distribute loads.[1] However, cartilage damaged by trauma, disease, or natural aging exhibits poor ability to heal due in part to its avascular nature, and this leads to functional morbidity for the individual and loss of productivity for society as a whole. Indeed, forces outside the physiological range of normal activity or a pathology-related inability of cartilage to manage normal loads are sufficient to produce focal cartilage defects and initiate cartilage degeneration, which can lead to osteoarthritis (OA), a disease that affects 9%-10% of the US population and results in a loss of the cartilage matrix due to an imbalance between matrix degradation and synthesis by the chondrocytes within the tissue.[2] Despite the prevalence of these focal cartilage defects and degenerative joint conditions, there exist no methods that provide restoration and regeneration of native articular cartilage. Thus, the development of effective and efficient techniques to remediate cartilage defects are urgently needed, especially given the increasing prevalence of obesity and aging demographics, both of which contribute to the occurrence of OA.

In examining surgical approaches to treat cartilage defects, specific attention should be paid to the potential of tissue engineering.[3] Tissue engineering is based on the following 3 key pillars: cells, growth factors, and scaffolds (Fig. 1). By using appropriate cell types with biologically appropriate signaling molecules and scaffolds based on our understanding of the tissue structure and its development, tissue engineering aims to recreate and restore native tissue architecture. Furthermore, it must be taken into account that cells, growth factors, and scaffolds all interact synergistically, with cells acting as the functional components whereas growth factors and environmental cues both direct as well as provide a permissive environment for cellular growth, proliferation, and maturation. Many of the basic principles of tissue engineering are found in current techniques applied in the surgical treatment of cartilage defects.

Clinical Treatment of Focal Cartilage Defects

Some of the oldest and traditionally used methods to stimulate endogenous cartilage healing include Pridie drilling,

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microfracture, and abrasion chondroplasty, all of which employ the recruitment of autologous bone marrow mesenchymal stem cells (BMSCs) that reside underneath the subchondral bone (Fig. 2). These BMSCs have been shown to have the ability to differentiate into many lineages, including cartilage, fat, and bone, and they also play an active role in wound healing when they are recruited to a site of tissue damage.[4,5] The extravasated blood from these procedures subsequently forms a clot and allows fibrin to act as a scaffold for these BMSCs. Although these techniques present improved patient outcomes compared with untreated defects, histologic studies demonstrate the formation of fibrocartilaginous tissue, which neither encourages host-tissue integration nor provides adequate mechanical support and ultimately results in the early development of OA.[6,7]

Given the inability of marrow stimulation procedures to provide for hyaline cartilage regeneration, newer techniques involving different cell types have been explored (Table). A source that gained much attention in the 1990s was the resident chondrocytes within cartilage itself. In 1994, Brittberg et al introduced Autologous Chondrocyte Implantation (ACI), an innovative procedure that consists of 2 stages: (1) isolating and culture-expanding autologous chondrocytes from non-weight-bearing regions of the articular surface and (2) injecting the *ex vivo* expanded chondrocytes into the defect site followed by closure with a periosteal flap to secure the cells (Fig. 2).[8,9] In the past 20 years, clinical studies of ACI have shown positive results,[10-20] but nevertheless randomized controlled trials and meta-analyses have failed to provide enough evidence to support the benefit of ACI when compared with marrow stimulation or osteochondral allograft implantation.[21-24] In addition, there are a host of considerations to take into account when using this approach. Related to the surgical procedure, periosteal flap morbidity and *in situ* flap hypertrophy have been reported.[25] To eliminate this periosteal-related complication, a study used a collagen membrane in its place, and at 2-year follow up less symptomatic periosteal hypertrophy in the collagen patch group was observed.[26] On the cellular side, autologous chondrocyte isolation and expansion suffers from low numbers of autologous chondrocytes available for harvest, dedifferentiation of chondrocytes during the expansion process, and donor site morbidity at the harvest site.[27] Lastly, in many cases the newly regenerated cartilage that results following ACI demonstrates fibrocartilage phenotype rather than hyaline cartilage.[28,29] Nevertheless, ACI is the only cell-based procedure approved by the US Food and Drug administration (FDA) to treat focal cartilage defects.

Although direct application of expanded autologous chondrocytes isolated through ACI remains the only FDA approved cell-based therapy for focal cartilage defects, there are a number

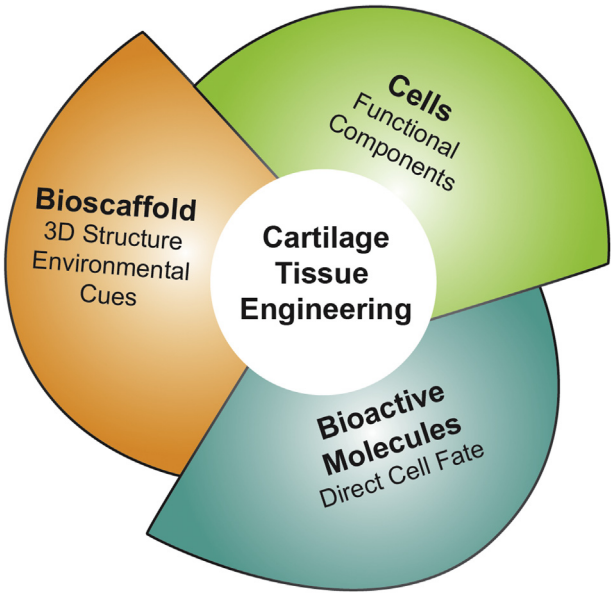

Figure 1 *Tissue engineering*. Tissue engineering is based on the following 3 key pillars: cells, growth factors, and scaffolds. These facets interact synergistically, with cells acting as the functional components whereas growth factors and environmental cues both direct as well as provide a permissive environment for cellular growth, proliferation, and maturation. Many of the basic principles of tissue engineering are found in current techniques applied in the surgical treatment of cartilage defects. (Color version of figure is available online.)

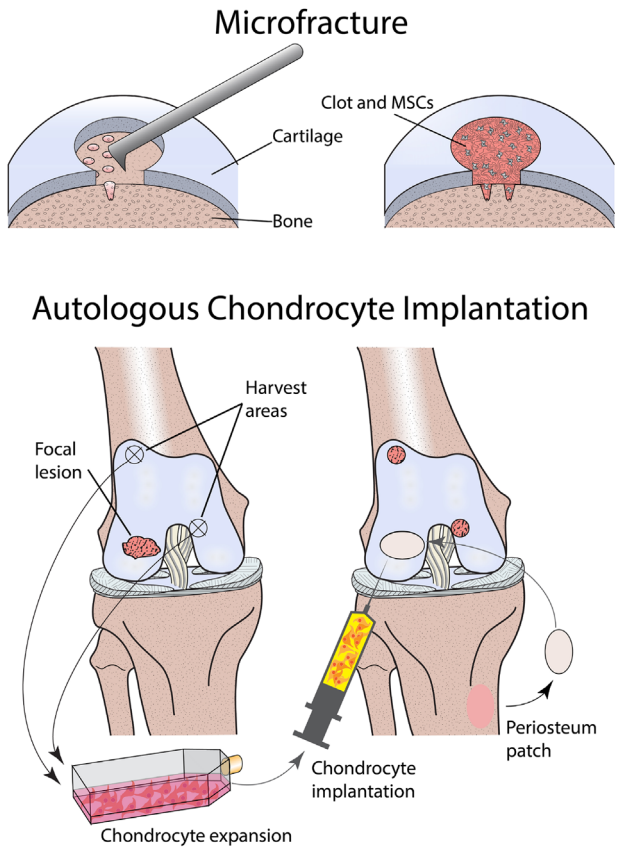

Figure 2 *Microfracture and autologous chondrocyte implantation (ACI)*. Microfracture (top) involves the recruitment of autologous bone marrow mesenchymal stem cells (BMSCs) that reside underneath the subchondral bone. The extravasated blood from these procedures subsequently forms a clot and allows fibrin to act as a scaffold for these BMSCs. ACI (bottom) involves the harvest of chondrocytes from non-weight-bearing regions of the articular surface followed by *in vitro* expansion and subsequent injection into the defect site. A periosteal flap is used to cover the defect. (Color version of figure is available online.)